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IMMUNE STATUS IN THE ACUTE PERIOD OF ISCHEMIC STROKE

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SUMMARY

In order to study the effectiveness of reflexotherapy in correction of immunological disorders in an acute period of ischemic stroke, 45 patients were clinical and immunological examined (on the 2nd day of patients's stay in hospital and 15 days after the beginning of the course of early rehabilitation). In the main group of patients (30 people), whose basic complex of rehabilitation measures was optimized by the inclusion of reflexotherapy, there was a significant improvement in a number of indicators of cellular and humoral immunity: reduction of leukocytes in peripheral blood ($p < 0.05$), an increase in lymphocyte count ($p < 0.05$), relative and absolute values of T-lymphocytes (CD3+) content ($p < 0.01$ and $p < 0.05$, respectively), immunoregulatory cells of T-helpers (CD4+) ($p < 0.05$), decrease in the number of B-lymphocytes to normal values ($p < 0.01$), and an increase in IgG level ($p < 0.05$). In the control group (15 people), where standard treatment was conducted, there was no pronounced dynamics of the indices. Thus, a comprehensive clinical and immunological study of the effectiveness of non-drug correction of immunological disorders in the acute period of ischemic stroke demonstrated high efficiency of acupuncture, with relative simplicity and safety of its application.

Key words

acute period of ischemic stroke, acupuncture, reflexotherapy, immune status, cellular and humoral immunity.

РЕЗЮМЕ

С целью изучения эффективности рефлексотерапии в коррекции иммунологических нарушений в остром периоде ишемического инсульта выполнено клиничко-иммунологическое обследование 45 пациентов (на 2-е сутки пребывания пациентов в стационаре и через 15 дней от начала курса ранней реабилитации). В основной группе пациентов (30 человек), у которых базовый комплекс реабилитационных мероприятий был оптимизирован включением рефлексотерапии, отмечено достоверное улучшение ряда показателей клеточного и гуморального иммунитета: снижение лейкоцитов в периферической крови ($p < 0,05$), повышение содержания лимфоцитов ($p < 0,05$), относительных и абсолютных показателей содержания Т-лимфоцитов (CD3+) ($p < 0,01$ и $p < 0,05$, соответственно), иммунорегуляторных клеток Т-хелперов (CD4+) ($p < 0,05$), снижение количества В-лимфоцитов до нормальных величин ($p < 0,01$) и повышение уровня IgG ($p < 0,05$). В контрольной группе (15 человек), где проводилось стандартное лечение, настолько выраженной динамики показателей не наблюдалось. Таким образом, проведенное комплексное клиничкоиммунологическое исследование эффективности немедикаментозной коррекции иммунологических нарушений в остром периоде ишемического инсульта показало высокую эффективность иглорефлексотерапии, при относительной простоте и безопасности ее применения.

Ключевые слова

острый период ишемического инсульта, акупунктура, рефлексотерапия, иммунный статус, клеточный и гуморальный иммунитет.

ИШЕМИК ИНСУЛТНИНГ ЎТКИР ДАВРИДА ИММУН СТАТУС ҲОЛАТИ

Ишемик инсултнинг ўткир даврида иммунологик бузилишларни даволашда рефлексотерапия самарадорлигини ўрганиш учун 45 беморни клиник ва иммунологик текширишдан ўтказилди (бемор касалхонада бўлганининг 2-кунида ва эрта реабилитациядан 15 кун ўтгач).

Рефлексотерапияни амалга ошириш орқали реабилитация тадбирларининг асосий комплекси оптималлаштирилган беморларнинг асосий гуруҳида (30 киши) хужайра ва гуморал иммунитетнинг бир қатор кўрсаткичлари сезиларли даражада яхшиланганлиги қайд этилди: периферик қонда лейкоцитларнинг камайиш ҳолати ($p < 0.05$), лимфоцитлар миқдорининг кўпайиши ($p < 0.05$), Т-лимфоцитлар сонининг нисбий ва мутлақ кўрсаткичлари (СД3+) (мос равишда $p < 0.01$ ва $p < 0,05$), иммунорегуляцион Т-хелпер хужайралари (СД4+) ($p < 0,05$), В-лимфоцитлар сони меъерий қийматларга ($p < 0, 01$) ва IgG даражасининг ошиши ($p < 0,05$) кузатилди. Стандарт даволаш амалга оширилган назорат гуруҳида (15 киши) ушбу кўрсаткичларнинг бундай аниқ динамикаси кузатилмади.

Шундай қилиб, ишемик инсултнинг ўткир даврида иммунологик бузилишларни доридармонсиз меъёрлаштириш самарадорлигини ҳар томонлама клиник ва иммунологик ўрганиш иглорефлексотерапиянинг юқори самарадорлигини, уни қўллашнинг нисбатан соддалиги ва хавфсизлигини кўрсатди.

Калит сўзлар

ишемик инсултнинг ўткир даври, акупунктура, рефлексотерапия, иммун статус, хужайравий ва гуморал иммунитет

Due to the high mortality rate after a stroke, it remains one of the highest in the world [10], optimization of early rehabilitation of strokes has acquired particular importance in recent decades. Moreover, in 68% of cases, the cause of death in patients who have suffered a stroke over the age of 60 is complications that join the main pathological process, whereas the immediate severity of stroke is only in 32% [2, 3]. In the very near term after the occurrence of the most severe forms of stroke, complications develop due to gross extensive damage to brain structures. Somatic complications caused by immobility of patients, vegetative dysfunction and infection develop at a relatively later date [2], therefore their prevention and treatment are of paramount practical importance.

In recent years, immunological mechanisms have played an important role in the pathogenesis of ischemic stroke, since the interaction of the nervous and immune systems, carried out on the principle of mutual regulation, determines the risk of disruption of the functions of one of them in the pathology of the other [6, 8, 11], aggravating the clinical picture and contributing to neurological deficiency. One of the main autoimmune processes in the pathogenesis of stroke is damage to the vascular wall endothelium, which occurs with the participation of immune factors and is associated with the settling of immune complexes on the inner surface of blood vessels [1].

The literature describes mainly various medicinal methods of correction of immunological disorders in patients who have suffered an ischemic stroke: recombinant IL-2 (roncoleukin) [5], cortexin [9], tactivin [7]. For effective rehabilitation of patients with arterial hypertension who have suffered an ischemic stroke, a combined application of the method of hyperbaric oxygenation in the standard mode and immunoprotection with actovegin according to the standard scheme in the basic complex of restorative treatment is proposed [4]. However, in

addition to the high cost of immunomodulating drugs, there is a risk of side effects when using them, which can significantly limit their use.

The centuries-old experience of acupuncture allows us to classify it as methods that restore the immune status.

The aim of the study was to study the possible effectiveness of reflexotherapy in the correction of immunological disorders in the acute period of ischemic stroke.

Materials and methods of research

A clinical and immunological examination of 45 patients (22 women and 23 men) in the acute period of ischemic stroke who were treated in the neuro-intensive care unit for patients with acute cerebral circulatory disorders of the Bukhara branch of the RCMP was performed.

The age of the patients ranged from 44 years to 81 years (the average age was 64.3 ± 1.8 years). Stroke was diagnosed in 12 patients in the basin of the left medial cerebral artery, in 18 – in the basin of the right medial cerebral artery, in 15 – in the vertebrobasilar basin.

The clinical diagnosis was made on the basis of anamnestic information, the results of subjective and objective neurological symptoms, and data from additional research methods (computed tomography of the brain, duplex scanning of the main arteries of the head, analysis of cerebrospinal fluid) in accordance with ICD 10 revision. The severity of neurological symptoms assessed on the NIHSS scale averaged 6.05 ± 0.42 points.

To assess the possible effect of acupuncture on the immune status indicators, a clinical and immunological study was conducted in two groups of patients, representative by gender, age and severity of neurological symptoms (Table 1).

Patients of the control group (15 people) received only standard therapy (medication, physiotherapy, physical therapy). In the patients of the main group (30 people), the basic therapy was optimized by the inclusion of reflexology.

At the same time, in order to correct immunological disorders, acupuncture points with immunoregulatory effects were pricked daily (in addition to the standard scheme of acupuncture, which was compiled depending on the existing neurological deficit): on the channels of the large intestine (GI(II) 11 Qu-chi, GI(II) 4 He-gu), stomach (E(III) 36 Zu-sanli), spleen (RP(IV) 6 San-yin-jiao), kidneys (R(VIII) 3 Tai-si), san-jiao (TR(X) 5 Wai-guan), liver (F(XII) 3 Tai-chun) (from two sides) and the anterior median meridian (J(XIV) 17 Tan-zhong and J(XIV) 6 Qihai).

Additionally, the points on the auricle (22, 55 and 101) were indicated on one side, alternating the sides of the impact (day on the right, day on the left). Reflexotherapy procedures were prescribed from 2-3 days of the patient's stay in the hospital (in the absence of contraindications), the duration of exposure was 20-30 minutes by the harmonizing method, the course consisted of 10-12 procedures.

Table 1

Characteristics of patients

Sign	Main group (n=30)	Control group (n=15)	p
Age, years	62,4±1,45	64,4±2,14	>0,05

Gender Husband/Wife, %		50,0/50,0	53,3/46,7	>0,05
Stroke localization, %	eft middle cerebral artery	23,3	26,6	>0,05
	basin right middle cerebral artery	40,0	33,3	
	basin vertebrobasilar basin	36,6	40,0	
Severity of neurological symptoms on the NIHSS scale, points		6,03±0,48	6,06±0,8	>0,05

The immunological study was conducted on the second day of the patients' stay in the hospital and 15 days after the start of the early rehabilitation course. Mononuclear cells were isolated from venous blood at a density gradient of ficoll–verografin ($p=1,077$).

Phenotyping of peripheral blood lymphocytes was performed by indirect immunofluorescence using monoclonal antibodies to CD3+, CD4+, CD8+, CD20+, CD16+, CD25+ differentiation clusters (Institute of Human Immunology and Genomics of the Republic of Uzbekistan), the fluorescent label FITZ (fluoresceinate isothiocyanate) was used.

The smears were counted using a luminescent microscope Lumam-P8, using a combination of light filters. The concentration of serum immunoglobulins was determined by Mancini radial immunodiffusion using monospecific antiserums. The indicators of 20 practically healthy individuals, representative by gender and age, were used as normative values.

Statistical data processing was carried out using the Microsoft Office 2013 (Excel) and Statistica 6.0 software package. Quantitative variables are presented as an average value \pm standard error of the average value ($X \pm mx$), the Student's t-test was used to assess the statistical significance of the observed differences.

Research results and their discussion

In the control group, on the 15th day of inpatient treatment, there was a tendency ($p<0,05$) to a slight decrease in leukocytes and lymphocytes in peripheral blood, compared with the results obtained at the beginning of treatment (Table 2).

There was also an unreliable increase ($p>0,05$) in the content of the relative number of T-lymphocytes (CD3+). The difference between the quantitative characteristics of CD4+ and CD8+ subpopulation indices before and after treatment was also not significant ($p>0,05$). There was a tendency to increase the content of NK cells (CD16+) and CD25+ ($p > 0,05$).

The dynamics of the state of humoral immunity is represented by a significant ($p>0,05$) decrease in elevated B-lymphocyte counts (CD20+) to the norm and a slight tendency to increase IgA and IgG, the IgM content practically did not change ($p>0,05$). Thus, a comparative analysis of the immunological examination in the control group showed that there were no significant changes in the immune status against the background of the generally accepted standard treatment of ischemic stroke.

In the main group of patients in whom the basic complex of rehabilitation measures was optimized by the inclusion of reflexotherapy (Table. 3), there was a significant decrease in

leukocytes in peripheral blood ($p < 0.05$) and a significant increase in the content of lymphocytes ($p < 0.05$).

There was also a significant increase in relative and absolute indicators of the quantitative content of T-lymphocytes (CD3+) ($p < 0.01$) and immunoregulatory T-helper cells (CD4+) ($p < 0.05$). There was a tendency to increase the indicators of cytotoxic T-lymphocytes (CD8+), natural killers (NK cells, CD16+), IRI and a tendency to decrease CD25+ cells expressing receptors for IL-2 ($p < 0,05$).

On the part of the humoral link of immunity, there was a significant ($p < 0.01$) decrease in the number of B lymphocytes to normal values with an unexpressed dynamics of an increase in IgA production ($p > 0.05$) and a significant increase in IgG levels ($p < 0.05$). Thus, almost all indicators of the immune status under the influence of treatment using acupuncture approached normal values. Normalization of the content of lymphocytes, T-lymphocytes (CD3+), T-helper cells (CD4+) and B-lymphocytes in peripheral blood is especially indicative.

Whereas in the control group, where standard treatment was carried out, there was no such pronounced dynamics of indicators, and such important indicators of immune status as T-lymphocytes (CD3+), T-helper cells (CD4+), NK cells (CD16+) remained below normal.

Table 2

Indicators of immune status in the control group before and after treatment

Indicators	Before treatment	After treatment	p
Leukocytes, $10^9/l$	6,96±0,97	6,10±0,7	>0,05
Lymphocytes, %	27,10±5,90	26,90±2,5	>0,05
T-lymphocytes (CD3+), %	47,80±0,70	48,80±0,60	>0,05
T-lymphocytes (CD3+), $\times 10^9/l$	0,77±0,13	0,71±0,06	>0,05
B-lymphocytes (CD20+), %	17,27±3,80	10,80±1,4	<0,05
B-lymphocytes (CD20+), $\times 10^9/l$	0,31±0,20	0,10±0,01	<0,05
T-helpers (CD4+), %	33,10±0,55	35,0±0,46	>0,05
T-helpers (CD4+), $\times 10^9/l$	0,71±0,08	0,77±0,04	>0,05
T-cytotoxic/suppressors (CD8+), %	15,10±0,44	15,50±0,63	>0,05
T-cytotoxic/suppressors (CD8+), $\times 10^9/l$	0,47±0,04	0,46±0,03	>0,05
IRI	2,11±0,04	2,07±0,08	>0,05
NK (Natural Killers) (CD16+), %	7,0±0,33	6,88±0,29	>0,05
CD25+, %	9,0±0,76	9,63±0,65	>0,05

IgA, g/l	1,46±0,06	1,51±0,06	>0,05
IgM, g/l	1,23±0,04	1,25±0,03	>0,05
IgG, g/l	13,40±0,26	13,70±0,18	>0,05

Table 3

Indicators of immune status in the main group of patients receiving acupuncture before and after treatment

Indicators	Before treatment	After treatment	p
Leukocytes, 10 ⁹ /l	7,60±0,72	6,0±0,60	<0,05
Lymphocytes, %	28,60±2,44	34,33±1,80	<0,05
T-lymphocytes (CD3+), %	47,40±0,90	52,90±1,0	<0,01
T-lymphocytes (CD3+), ×10 ⁹ /l	0,82±0,09	1,10±0,10	<0,05
B-lymphocytes (CD20+), %	17,17±2,80	10,20±1,50	<0,01
B-lymphocytes (CD20+), ×10 ⁹ /l	0,24±0,11	0,15±0,02	<0,05
T-helpers (CD4+), %	32,70±0,59	38,67±0,66	<0,05
T-helpers (CD4+), ×10 ⁹ /l	0,92±0,07	1,0±0,08	>0,05
T-cytotoxic/suppressors (CD8+), %	15,50±0,36	16,38±0,45	>0,05
T-cytotoxic/suppressors (CD8+), ×10 ⁹ /l	0,54±0,03	0,64±0,04	>0,05
IRI	2,04±0,05	2,12±0,06	>0,05
NK (Natural Killers) (CD16+), %	7,39±0,29	8,20±0,41	>0,05
CD25+, %	9,70±0,53	9,10±0,45	>0,05
IgA, g/l	1,46±0,08	1,54±0,07	>0,05
IgM, g/l	1,24±0,03	1,29±0,04	>0,05
IgG, g/l	12,80±0,32	13,90±0,36	<0,05

Against the background of a significant improvement in the immune status indicators in the main group, there was a more significant regression of neurological deficit on the NIHSS scale by an average of 4.6 points (up to 1.43 ± 0.14 points, $p < 0.001$), while in the control group there was less pronounced positive dynamics – by 2.6 points (up to 3.5 ± 0.54 , $p < 0.05$). There were no complications during reflexotherapy procedures.

Thus, a comprehensive clinical and immunological study of the effectiveness of non-drug correction of immunological disorders in the acute period of ischemic stroke showed high effectiveness of acupuncture, with relative simplicity and safety of its use. Correction of immunological disorders in the acute period of ischemic stroke is very important, because it is a prevention of the development of infectious complications, and, consequently, accelerates the process of early rehabilitation.

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